

at 2.5 mL/min into 2 liters of a stirred solution that consisted of 0.1.2% lecithin and 2.2% glycerin. No other surface modifiers were added. The surfactant system was buffered at pH=8.0 with 5 mM tris buffer and the temperature was held at 0° to 5° C. during the entire precipitation process. The post-precipitated dispersion was next homogenized cold (5–15° C.) for 20 passes at 10,000 psi. Following homogenization, the NMP was removed by centrifuging the suspension, removing the supernatant, and replacing the supernatant with fresh surfactant solution. This post-centrifuged suspension was then rehomogenized cold (5–15° C.) for another 20 passes at 10,000 psi. The particles produced by this process had a mean diameter of 0.927 μ m with 99% of the particles being less than 2.36 μ m.

Example 11

Preparation of Nabumetone Suspension by use of Process Category 3, Method B with Homogenization

Surfactant (2.2 g of poloxamer 188) was dissolved in 6 mL of N-methyl-2-pyrrolidinone. This solution was stirred at 45° C. for 15 minutes, after which 1.0 g of nabumetone was added. The drug dissolved rapidly. Diluent was prepared which consisted of 5 mM tris buffer with 2.2% glycerol, and adjusted to pH 8. A 100-mL portion of diluent was cooled in an ice bath. The drug concentrate was slowly added (approximately 0.8 mL/min) to the diluent with vigorous stirring. This crude suspension was homogenized at 15,000 psi for 30 minutes and then at 20,000 psi for 30 minutes (temperature=5° C.). The final nanosuspension was found to be 930 nm in effective mean diameter (analyzed by laser diffraction). 99% of the particles were less than approximately 2.6 microns.

Example 12

Preparation of Nabumetone Suspension by use of Process Category 3, Method B with Homogenization and the use of Solutol® HS 15 as the Surfactant

Replacement of supernatant liquid with a phospholipid medium.

Nabumetone (0.987 grams) was dissolved in 8 mL of N-methyl-2-pyrrolidinone. To this solution was added 2.2 grams of Solutol® HS 15. This mixture was stirred until complete dissolution of the surfactant in the drug concentrate. Diluent was prepared, which consisted of 5 mM tris buffer with 2.2% glycerol, and which was adjusted to pH 8. The diluent was cooled in an ice bath, and the drug concentrate was slowly added (approximately 0.5 mL/min) to the diluent with vigorous stirring. This crude suspension was homogenized for 20 minutes at 15,000 psi, and for 30 minutes at 20,000 psi.

The suspension was centrifuged at 15,000 rpm for 15 minutes and the supernatant was removed and discarded. The remaining solid pellet was resuspended in a diluent consisting of 1.2% phospholipids. This medium was equal in volume to the amount of supernatant removed in the previous step. The resulting suspension was then homogenized at approximately 21,000 psi for 30 minutes. The final suspension was analyzed by laser diffraction and was found to contain particles with a mean diameter of 542 nm, and a 99% cumulative particle distribution sized less than 1 micron.

While specific embodiments have been illustrated and described, numerous modifications come to mind without departing from the spirit of the invention and the scope of protection is only limited by the scope of the accompanying claims.

What is claimed is:

1. A method for preparing submicron sized particles of an organic compound, the solubility of which is greater in a water-miscible first solvent than in a second solvent which is aqueous, the process comprising the steps of

- (i) dissolving the organic compound in the water-miscible first solvent to form a solution, the first solvent being selected from the group consisting of N-methyl-2-pyrrolidinone, 2-pyrrolidone, dimethyl sulfoxide, dimethylacetamide, lactic acid, methanol, ethanol, isopropanol, 3-pentanol, n-propanol, glycerol, butylene glycol, ethylene glycol, propylene glycol, mono- and diacylated monoglycerides, dimethyl isosorbide, acetone, dimethylformamide, 1,4-dioxane, polyethylene glycol, polyethylene glycol esters, polyethylene glycol sorbitans, polyethylene glycol monoalkyl ethers, polypropylene glycol, polypropylene alginate, PPG-10 butanediol, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, PPG-15 stearyl ether, propylene glycol dicaprylate, propylene glycol dicaprate, propylene glycol laurate;
- (ii) mixing into the solution a first surface modifier selected from the group consisting of anionic surfactants, cationic surfactants and nonionic surfactants;
- (iii) mixing into the second solvent, a second surface modifier to define a second solution, the second surface modifier selected from the group consisting of: anionic surfactants, cationic surfactants and nonionic surfactants; and
- (iv) mixing the first solution with the second solution with high energy agitation by homogenization, counter-current flow homogenization, or microfluidization to define a pre-suspension of non-spherical, crystalline particles having an average effective particle size of less than 2 μ m.

2. The method of claim 1 further comprising the step of mixing into the second solution a phospholipid.

3. The method of claim 2 wherein the phospholipid is selected from natural phospholipids and synthetic phospholipids.

4. The method of claim 2 wherein the phospholipid is selected from the group consisting of phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, phosphatidylinositol, phosphatidylglycerol, phosphatidic acid, lysophospholipids, egg phospholipid and soybean phospholipid.

5. The method of claim 1 wherein the nonionic surfactant is selected from the group consisting of polyoxyethylene fatty alcohol ethers, sorbitan fatty acid esters, polyoxyethylene fatty acid esters, sorbitan esters, glycerol monostearate, polyethylene glycols, cetyl alcohol, ceto-stearyl alcohol, stearyl alcohol, poloxamers, polaxamines, methylcellulose, hydroxycellulose, hydroxy propylcellulose, hydroxy propylmethylcellulose, noncrystalline cellulose, polyvinyl alcohol, polyvinylpyrrolidone, glyceryl esters, and phospholipids.

6. The method of claim 1 wherein the anionic surfactant is selected from the group consisting of potassium laurate, triethanolamine stearate, sodium lauryl sulfate, sodium dodecylsulfate, alkyl polyoxyethylene sulfates, sodium alginate, dioctyl sodium sulfosuccinate, phosphatidyl glycerol, phosphatidyl inositol, phosphatidylserine, phosphatidic acid and their salts, sodium carboxymethylcellulose, bile acids and their salts and calcium carboxymethylcellulose.

7. The method of claim 1 wherein the cationic surfactants are selected from the group consisting of quaternary ammo-